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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/510,562	02/22/2000	Gerard Housey	395/35	3061

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KENYON & KENYON
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
GUZO, DAVID	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 10/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/510,562	HOUSEY, GERARD	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33,34,36,37,43-50,59-65,71-78 and 87-120* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33,34,36,37,43-50,59-65,71-78 and 87-120* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/10/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

SOP

Detailed Action

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/14/05 has been entered.

35 USC 112, 1st Paragraph (New Matter) Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33-34, 36-37, 43-50, 59-65, 71-78 and 87-120 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant has amended the claims to recite that the level of the target enzyme in the cell in the presence of the potential inhibitor or activator is maintained such that the cell remains capable of exhibiting the phenotypic response following removal of the potential direct inhibitor or activator.

There is no support in the specification for limitations concerning the level of the target enzyme in the cell when in contact with the potential inhibitor or activator. The instant claims, as currently drafted, would specifically exclude circumstances wherein the target enzyme is irreversibly bound to the potential inhibitor and/or is destroyed and hence the level of said enzyme cannot be **maintained** such that the cell remains capable of exhibiting the phenotypic response to the potential inhibitor. This is a NEW MATTER rejection.

Applicant has traversed the previous new matter rejection by asserting that the instant amendment renders the new matter rejection moot. **Applicant currently asserts that the instant claims only require that the POI be enzymatically active before the inhibitor is added and after the inhibitor is removed.**

Applicant's arguments filed 7/14/05 have been considered but are not persuasive. Contrary to applicant's arguments, the claims appear to require that **the level of the enzyme** be maintained before the potential inhibitor is added, during the period the potential inhibitor is present and after the potential inhibitor is removed.

It is noted that the limitation concerning the level of the enzyme being maintained in the cell was added (in the amendment filed 5/19/03) to obviate an art rejection (over Drebin et al.) wherein Drebin et al. specifically taught the claimed method wherein the inhibitor (an antibody) bound to the target enzyme and inactivated (destroyed) said enzyme. In traversing the rejection over Drebin et al., applicant asserted that the then newly added claim limitation concerning maintaining the level of the enzyme specifically

excluded embodiments wherein the level of the POI was reduced by binding to an inhibitor. Applicant, in the Remarks filed 5/19/03, asserted that:

> Most importantly, the significance of providing an appropriate test cell capable of maintaining a functional level of the POI in the presence of the chemical agent is discussed in detail in the specification, for example, at page 35, line 15 through page 36, line 5 (Example 1; 1281 patent, col. 16, lines 45-55), wherein it is explained that normal cells, upon activation of the enzyme PKC by the chemical agent TPA, "down-regulate" or "down-modulate" PKC, and thus become refractory to further stimulation. Such down regulation of PKC upon stimulation was known in the art. (See, e.g., Boreiko et al., 1980, Cancer Res. 40, 4709-16, cited in the original specification, and of record in the instant application.). In contrast, Applicant's test cells that maintain high levels of PKC (e.g., constitutive production) are demonstrated to respond to TPA in a repetitive manner and do not become refractory. Stable expression of the POI leads to a measurable / observable change in morphology of the cells in response to treatment with the PKC activator TPA that continues to be sensitive to subsequent treatments with TPA. Applicant's test cell remains responsive following treatment with an active chemical agent. In contrast Drebin teaches that p185 is sufficiently down-modulated following exposure to the antibody that the cells lose their phenotype altogether (see, e.g., Drebin, page 697, Fig. 3B, page 699, Fig. 6, and discussion therein).
>
> Applicant points out, however, that the level of the enzyme need not remain exactly the same in the presence of the chemical test agent. It is sufficient that the enzyme be maintained at a high level in the test cell relative to the control cell such that modulation of the responsive change in the phenotypic characteristic by inhibitors and activators can be observed or measured. (Remarks filed 5/19/03, pp. 8-9).

In view of applicant's current argument that the claims only require that the POI (enzyme) be enzymatically active before the inhibitor is added and after the inhibitor is removed, the 35 USC 102(b) rejection over Drebin et al. is re-applied (See below).

35 USC 102 Rejections

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 33-34, 36, 43-44, 46-47, 49, 63-64, 71-72, 74-75, 77, 88, 90-92, 94-95, 97-98, 100, 106-107, 109-110, 112-113, 115 and 118 are rejected under 35 U.S.C. 102(b) as being anticipated by Drebin et al.

Applicants and Drebin et al. (Cited by applicants, Cell, Vol. 41, 1985, pp. 695-705, see whole article, particularly the results section on pp. 696-698 and pp. 700-701) both recite the same method whereby a direct inhibitor of a target enzyme is identified. Drebin et al. recite a method comprising determining whether a chemical agent (i.e. an antibody) directly interacts with a protein or enzyme (i.e. *neu*-oncogene product, p185, expressed by a vector transfected into the cell) in a cell wherein expression of the p185 protein in the cell evokes a responsive change (i.e. a graded response) in a phenotypic characteristic of the cell (anchorage independent growth) other then the level of the enzyme in the cell by providing a first mammalian cell which overproduces the protein or enzyme and exhibits said phenotypic response to the enzyme and a second mammalian cell which produces the protein or enzyme at a lower level or not at all compared with the first cell line, incubating the chemical agent with both cell lines and comparing the phenotypic response of the cell lines to determine if the agent is an inhibitor of the protein or enzyme. The antibodies disclosed by Drebin et al. are contemplated for use in contacting cells expressing oncogene products and for use in treating malignancies. Drebin et al. therefore teaches the claimed invention. Drebin et al. notes that the level of the enzyme is maintained such that the cell is capable of expressing p185 and exhibiting the phenotypic response (i.e. anchorage independent

growth) after removal of the inhibitor. The p185 enzyme is enzymatically active before the inhibitor is added and the portion of the p185 enzyme in the cell which is not bound by the antibody and/or newly produced after the inhibitor is removed is enzymatically active and hence the level of the enzyme is maintained such that the cell remains capable of exhibiting the phenotypic response following removal of the inhibitor. Drebin et al. therefore teaches the claimed invention.

35 USC 112, 1st (Enablement) Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33-34, 36-37, 43-50, 59-65, 71-78 and 87-120 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is maintained for reasons of record in the previous Office Action and for reasons outlined below.

Applicant traverses this rejection by asserting that the teachings of Hsiao et al. and Ledwith et al. cannot allegedly be used to illustrate the unpredictability of applicant's invention because neither Hsiao et al. nor Ledwith et al. practice the claimed method. Applicant asserts that neither Hsiao et al. nor Ledwith teaches the claimed

responsive phenotypic change or a graded cellular response. Applicant asserts that Hsiao et al. provides no means for determining whether any chemical agent directly or indirectly interacted with any cellular component. With regard to Ledwith et al., applicant asserts that the method disclosed by Ledwith et al. cannot be compared with applicant's invention because it is not capable of fully reverting the transformed phenotype that results from c-Ha-ras overproduction and because Ledwith et al. does not define a "responsive change" in a phenotypic characteristic as contemplated by applicant. Applicant asserts that the effectiveness of the claimed method was confirmed in the binding of tamoxifen to PKC. Applicant indicates that the direct binding of tamoxifen to PKC was confirmed after applicant's disclosed work by *in vitro* binding studies. Finally, with regard to false positive results, applicant asserts that a claim is not invalid because it encompasses some inoperative embodiments and applicant asserts that the claimed method has been in use in numerous laboratories and applicant is unaware of any false positive results.

Applicant's arguments filed 7/14/05 have been fully considered but they are not persuasive.

On an initial point, applicant's arguments revolve, in part, on the alleged special nature of the "responsive change" in a phenotype of the cell in response to production of the enzyme (POI) as defined in the instant application. However, an examination of the instant specification reveals that said specification does not even recite the term "responsive change", let alone define it, and therefore it must be given it's broadest

definition, i.e. any change in the cell phenotype in response to expression of the enzyme (POI).

Applicant's critique of the Hsiao et al. and Ledwith et al. references appears to miss the point. The Hsiao et al. and Ledwith et al. references are not being applied as prior art, they are only being used to illustrate the complex and unpredictable nature of the signaling pathways involved in cells and how use of phenotypic changes associated with expression of a target enzyme (POI) in a method for identifying direct inhibitors or activators of said target enzyme can actually result in identification of agents which do not interact with the target but instead interact (directly or indirectly) with another target.

Applicant critiques the Hsiao et al. and Ledwith et al. references because they allegedly do not practice the claimed invention. Applicant also reads limitations into the instant claims and then argues that the Hsiao et al. and Ledwith et al. references do not teach these limitations and hence cannot be used to show the unpredictability of applicant's invention. For example, one of the primary arguments of applicant is that Ledwith et al. does not show **complete reversion** of the transformed phenotype that results from c-Ha-ras ($p21^{ras}$) overproduction and that based upon this, the skilled artisan would not choose a compound that only partially reverts a selected phenotype that is fully driven by the activity of the true POI. An examination of the claims reveals that complete reversion of the transformed phenotype is not recited in the claims; indeed, the relevant claim limitation is that the chemical agent only needs to "exert a greater effect on the responsive change in the phenotype characteristic of the first cell line relative to the second" in order for it to be judged, by the claimed method, to be a

direct inhibitor or activator of the target enzyme. With regard to applicant's arguments that the skilled artisan would not choose a compound which only partially reverts the phenotypic response, said arguments are again not on point. The relevant issue at hand is if the skilled artisan practiced the **claimed invention**, would said skilled artisan identify as a direct inhibitor of $p21^{ras}$ compounds which actually bind to (and inhibit) c-fos. The answer must be yes because while expression in cells of $p21^{ras}$ evokes a responsive change (though inducing expression of c-fos) in a phenotypic characteristic of the cell and said cell is capable of exhibiting the phenotypic response prior to an inhibitor being added and after the inhibitor is removed, compounds which directly bind to c-fos would be identified as direct inhibitors of $p21^{ras}$. The only effect the test compound needs to exert is a greater effect on the responsive change in the phenotypic characteristic of the cells expressing the $p21^{ras}$ gene vs. the control cells. Clearly, Ledwith et al. show this. While the claimed invention may serve as a screen for identifying potential inhibitors or activators of a given target enzyme, further, undisclosed, procedures are required to determine exactly what molecule the potential inhibitor or activator is interacting with. Also, it is again noted that the Hsiao et al. and Ledwith et al. papers are cited merely to demonstrate the complex nature of biochemical pathways and the unpredictability of attempting to use phenotypic changes associated with expression of a target enzyme to identify direct inhibitors or activators of a target enzyme.

With regard to false positive results and the use of applicants' invention in numerous labs, it is assumed that the invention used in the numerous laboratories is the

invention claimed in the patents which have been issued from parent applications of the instant case. However, the claims in the patents previously issued to applicant are not the same as the claims in the instant case and therefore the instantly claimed invention has not been in use. Indeed, if applicant is asserting that the instant claims are not patentably distinct from the claims in the issued parent applications, the examiner will reject the instant claims under obviousness type double patenting over the claims in the issued patents. While applicant's invention can be useful as an initial screen for detecting compounds which interact, in some fashion, with the target enzyme or some target affecting expression of the target enzyme or some target in the biochemical pathway in which the target enzyme participates, the claimed invention cannot distinguish between compounds which directly bind to the target vs. compounds which interact in some other fashion with the target or molecules which in some way affect the target enzyme.

Also, the examiner is not stating that just because the claimed invention encompasses some inoperative embodiments, the claims are unpatentable. Rather, the grounds of rejection involve the inability of the skilled artisan to practice the claimed invention without having to practice undue and excessive experimentation in order to sort out what any result achieved actually means, i.e. is the test agent a direct inhibitor or activator of the POI or is it exerting its effect on the observed phenotypic changes by some other (indirect) mechanism(s).

With regard to whether the instant disclosure is sufficient to enable the skilled artisan to distinguish between direct vs. indirect inhibitors of the POI using applicant's

specification, the Decision of the Technical Board of Appeal of the European Patent Office in case T 0729/00 3.3.4 (concerning an issued parent of the instant application) is of significance. Specifically the Decision notes:

The patent referred only to distinguishing between substances which specifically inhibit the protein of interest and substances which affect cell morphology or growth by other mechanisms. ***If, as argued by the patentee, the invention was supposed to enable the user to distinguish between direct and indirect inhibitors, the information in the patent was insufficient for this to be achieved and certainly the technical features listed in the claim were insufficient for this result to be achieved*** (emphasis added). For example, it would not be possible to distinguish between a substance which bound to the gene coding for the protein of interest causing a reduction in its expression in the cell line, and a substance binding to the protein of interest and inhibiting its enzymatic activity. The observed phenotypic effect could well be the same, and other tests would be needed to distinguish the two cases.

With regard to the specific direct binding of tamoxifen to PKC, it is noted that direct binding of tamoxifen to PKC had to be confirmed by *in vitro* direct binding assays involving an immobilized analogue of tamoxifen. While applicant may have identified tamoxifen as an inhibitor of PKC using the instant methodology, whether it actually was a direct inhibitor of PKC had to be determined using an *in vitro* binding assay.

Claims 33-34, 36-37, 43-50, 59-65, 71-78 and 87-120 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is maintained for reasons of record in the previous Office Actions and for reasons outlined below.

Applicant traverses this rejection by again asserting that the specification teaches the elements that are essential for determining whether a chemical agent is a direct inhibitor or activator of an enzyme and applicant reiterates the same reasons in support thereof as recited in arguing the above enablement rejection.

Applicant's arguments have been fully considered but they are not persuasive. For the reasons cited in the above enablement rejection and for reasons of records, the rejection is maintained.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (571) 272-0767. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D., can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David Guzo
September 29, 2005

DAVID GUZO
PRIMARY EXAMINER